Blood Monitoring of Bezafibrate in a Chronic Hemodialysis Patient

K.	Kazuhito	Takeda
M.	Masahiko	Nakamoto
C.	Chikao	Yasunaga
G.	Gakusen	Nishihara
K.	Kenzo	Matsuo
M.	Marie	Urabe
T.	Tadanobu	Goya

Kidney Center, Saiseikai Yahata Hospital, Kitakyushu, Japan

Kazuhito Takeda, MD, Kidney Center, Saiseikai Yahata Hospital, 5-9-27 Harunomachi, Yahatahigashi-ku, Kitakyushu, Fukuoka 805 (Japan)

Dear Sir,

Bezafibrate is one of the common drugs used in the treatment of hyperlipidemia. Chronic dialysis patients often have hyperlipidemia but the drug is not suitable for such patients because it is mostly excreted in the urine, and is hardly dialyzed owing to its 90% binding to protein in blood. Rhabdo-myolysis or muscle damage due to bezafibrate is well known in chronic dialysis patients [1, 2]. The bezafibrate medication must be prohibited. We experienced a chronic dialysis patient who developed liver damage and rhabdomyolysis due to bezafibrate. We carefully followed up the patient by monitoring the blood bezafibrate levels. There are few reports on the monitoring of blood bezafibrate levels in patients with chronic renal failure.

A 49-year-old male who had been on maintenance hemodialysis for 10 years was referred from another hospital because of liver damage. He was admitted complaining of systemic severe myalgia, diarrhea, anorexia, and spike fever. Physical examination at the time of admission to our hospital revealed that he was not icteric, had no lymphadenopathy, his temperature was 37.8 °C, heart rate 84 beats/min, and blood pressure 130/80 mm Hg. Laboratory studies showed: hemoglobin 11.7 g/dl; hematocrit 33.7%; white blood cell count 7,400/μl; platelets $36.7 \times 10^4/\mu\text{l}$; aspartate amino-transferase 297 U/l; alanine aminotransferase 213 U/l; lactate dehydrogenase (LDH) 1,162 U/l, and creatine phosphokinase (CPK) 2,681 IU/l (MM type 100%). He was diagnosed as having rhabdomyolysis. It was not until his medical history was taken that we found out that the patient had been treated with bezafibrate. Seven days after the administration of bezafibrate the patient

Fig. 1. Changes in creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), and the serum concentration of bezafibrate.
(weeks)

Indeed bezafibrate was reduced only by about 20% by hemodialysis. The patient was restricted from exercises, and took rest. A week later, serum bezafibrate was reduced to an undetectable

level and the clinical symptoms resolved. CPK and LDH returned to normal values 2 weeks after bezafibrate was discontinued (fig. 1).

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E-Mail karger@karger.ch Fax+ 41 61 306 12 34 <http://www.karger.ch>

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Bezafibrate is a clobifibrate. Clobifibrates have a cholesterol and triglyceride lowering effect. They affect various points in the metabolic pathway of lipoproteins. They suppress very low density lipoprotein synthesis in the liver and increase the activity of lipoprotein lipase (LPL) and hepatic triglyceride lipase. As a result, high density lipoprotein cholesterol increases and low density lipoprotein decreases. Therefore clobifibrates decrease not only triglyceride but cholesterol levels. Bezafibrate is also known to inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and to improve hyperglycemia under insulin-resistant conditions [3]. Bezafibrate might be especially suitable for diabetic patients with secondary hypertriglyceridemia. After oral administration of bezafibrate, rapid absorption from the gastrointestinal tract leads to peak serum levels at 30 min and 2 h. Approximately 95% of the absorbed bezafibrate is excreted in the urine within 48 h [4]. Bezafibrate is not always a safe drug for patients with impaired renal function [1, 2, 5]. Chronic dialysis patients often also have lipid abnormalities. This is because long-term dialysis accumulates inhibitory substances against LPL and heparin consumes LPL. As dialysis patients fundamentally consume a low protein and high calorie diet, they tend to have hypertriglyceridemia. Bezafibrate is a nondialyzable drug owing to its 90% binding to protein in blood. In chronic dialysis patients, the serum concentration is markedly elevated even with small doses of bezafibrate, and prolonged high levels in serum persist [1, 2, 5], as was demonstrated in our patient. Though bezafibrate levels in serum are elevated to some degree in normal healthy people, high levels in serum do not persist because of the immediate excretion in urine [4]. It is certain that a prolonged high serum concentration of bezafibrate is correlated with muscle damage or rhabdomyolysis. As occurred in our patient, nausea, myalgia, and diarrhea were common side effects of bezafibrate. As the serum concentration declined, the clinical symptoms resolved. It is thought that not only muscle damage but other clinical symptoms are closely related to the prolonged high blood level of bezafibrate. When peritoneal dialysis patients were treated with bezafibrate of 400 mg/day (normal dose) for 3 weeks, all had muscle damage with CPK enhancement [1, 2]. Even at the recommended dosage, bezafibrate was reported to induce rhabdomyolysis or muscle damage. There have been few reports on the relationship between the serum concentration and side effects by monitoring the blood bezafibrate level. After discontinuing bezafibrate, it takes the drug about 1 week at least to be cleared from the blood in almost all chronic dialysis patients. Bezafibrate should never be used in chronic dialysis patients.

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